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Association Between Serum Zinc Concentration Levels And Severity Of Coronavirus Disease 2019 (Covid-19) In Japanese Inpatients

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Background: It has been reported that zinc deficiency is related to severe inflammatory conditions especially those of respiratory diseases. However, studies that have examined the association between the serum zinc concentration and the severity of coronavirus disease 2019 (COVID-19) are still limited. The aim of this study was to assess that association in Japanese inpatients with COVID-19.

Methods: This cross-sectional study, conducted from April 2020 to August 2021, included 467 eligible adult inpatients with COVID-19 whose serum zinc concentration was measured. Serum zinc concentration categories were defined as deficiency (< 60 μg/dL), marginal deficiency (≥ 60 to < 80 μg/dL), and normal (≥ 80 μg/dL). Multivariate logistic regression was used to assess the association between serum zinc deficiency and severe COVID-19. Serum zinc concentration levels were compared between mild and other severities of COVID-19 by Dunnett's method. The P for trend was estimated using the Jonckheere-Terpstra test.

Results: The proportions of subjects with serum zinc deficiency (< 60 μg/dL) and marginal zinc deficiency (≥ 60 to < 80 μg/dL) were 39.5% and 54.3% in women, and 36.4% and 57.0% in men, respectively. Serum zinc deficiency was significantly associated with severe COVID-19 compared to marginal deficiency and normal (odds ratio = 3.60, 95% confidence interval = 1.60–8.13, P < 0.01) after adjusting for confounders. An increase in severity of COVID-19 was inversely related to increases in serum zinc concentration levels (P < 0.01 for trend). Each serum zinc concentration of moderate and severe cases was also significantly lower compared with mild cases (P < 0.01).

Conclusion: The severity of COVID-19 was significantly related to serum zinc concentration levels. These results suggest the importance of considering the serum zinc concentration when treating patients with COVID-19.

Keywords: COVID-19, Zinc, severity, nutrition, epidemiology

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major healthcare burden worldwide. The pathogenesis of COVID-19 is not fully understood, but it is probably multifactorial, resulting in a systemic hyperinflammatory response and associated with thromboembolic complications in severe cases.[1,2]

It has been reported that those conditions such as obesity, hypertension and smoking status (current and past) are risk factors of severe COVID-19.[3–5] Progression of severity of COVID-19 are well recognized as the consequences to intense inflammatory cytokine storms, for which mechanisms are composed of multi factors including malnutrition. As immune systems need micronutrients as well as vitamins,[6] several reports were shown about those elements as potential therapeutic effects on COVID-19 patients.[7] From the early period of COVD-19-pandemic, zinc, which is one of the most important micronutrients, was regarded to have some roles in COVID-19 pathologies because some port of the

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patients presented taste disorders which is one of the representative symptoms of zinc deficiency. Recently, zinc has also received considerable attention as a factor associated with the severity of COVID-19.[8] Zinc is a trace element that is necessary for a wide range of biochemical, immunological, and clinical functions. It is well known that mild zinc deficiency may cause impaired taste and smell, skin disorders, and impaired vision. In addition, severe zinc deficiency may reduce immunity and is associated with an increased risk of pneumonia.[9–12]

However, studies that have examined serum zinc deficiency in COVID-19 patients among the Japanese population are limited. Therefore, surveys to assess the association between zinc deficiency and the severity of COVID-19 are much needed. The present study aimed to assess the serum zinc concentrations and examine the association of serum zinc levels with the severity of COVID-19 in Japanese patients.

Patients and Methods

Subjects

This cross-sectional study screened 514 Japanese adult (from 18-year-old to 100-year-old) in-patients who were admitted for the treatments for COVID-19 from April 2020 to June 2021 and discharged to August 2021 at the Juntendo University Hospital in Tokyo, Japan. Patients were registered in the study those who met the following eligibility criteria: 1) 18 years or older and 2) patients whose were treated with COVID-19. Patients, whose clinical data including serum zinc concentration levels were missing, were excluded from the study. Of these, 467 eligible inpatients whose serum zinc concentration was measured were included in the present study.

Variables

Height (m) and weight (kg) were each measured in the standing position if possible. For participants in severe cases, supine positioned height was measured using a polyvinyl chloride (PVC) measure tool and weight was measured by using a scaling bed which was equipped to the High Care Unit, where had supposed to admit the severe patients according to the own regulations of the hospital. Body mass index (BMI) was calculated by dividing body weight (kg) by height squared. (m2). Vital signs [blood pressure measurement (mmHg), heart rate (per minute), respiratory rate (per minute), and temperature (°C)] were evaluated at admission. Blood pressures were measured using a standard mercury sphygmomanometer from the right or left arm after the participant had rested in the sitting position if possible or supine position in severe cases.

Blood samples were collected on admission. Serum concentrations of total cholesterol (T-Cho), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were also measured. LDL-C was estimated using the Friedewald equation [(TC) – (HDL-C) – (TG/5)].[13] Hemoglobin A1c (HbA1c; National Glycohemoglobin Standardization Program) was measured by high-performance liquid chromatography using an automated analyzer. Total protein (TP), albumin (Alb), hemoglobin, high-sensitivity C-reactive protein (hs CRP), serum uric acid (SUA), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, and ferritin levels were measured. The estimated glomerular filtration rate (eGFR) was calculated using the Japanese GFR equation: eGFR (mL/min/1.73 m^2) = 194 × $Cr^{-1.094}$ × $age^{-0.287}$.[14] In addition, complete blood counts and D-dimer levels were measured.

The zinc levels were estimated to assess the nutritional condition for all inpatients at the admission. The serum zinc concentration was measured by a colorimetric method using a colorimetric reagent kit "ACCURAS AUTO Zn" (SHINO-TEST Corporation, Tokyo, Japan). The reagent was applicable to all auto-analyzers and widely used in Japanese hospital laboratories without any serum pretreatment. With-run and between-run precisions (C.V). were 0.7–1.0% and 1.4–1.9%, respectively. The calibration curve was linear up to 500 μg/dL, and the detection limit was 4 μg/dL. A good correlation between the method and that of atomic absorption spectrophotometry has been reported (r = 0.996).[15] As for the laboratory control, "NIST (SRM3168)" (SHINO-TEST Corporation) was used as the reference material. Participants or their families or representatives were interviewed to collect information on alcohol consumption, smoking habit, and medical history of comorbidities, such as diabetes mellitus, dyslipidemia, hypertension, cardiovascular disease, cerebrovascular disease, chronic kidney disease, cancer, and chronic obstructive pulmonary disease.

Based on the condition of the patients after hospital admission, all patients were classified into three groups: mild, moderate and severe cases. The classification criteria were based on the nine-score ordinal scale described in the World Health Organization (WHO) ordinal clinical severity scale that was collected at the time of hospital admission: (0) no clinical or biological evidence of infection; (1) no limitation of activities; (2) limitation of activities; (3) hospitalized, no oxygen therapy; (4) hospitalized, oxygen by mask or nasal prongs; (5) hospitalized, non-invasive ventilation or high-flow oxygen; (6) hospitalized, intubation, and mechanical ventilation; (7) hospitalized, ventilation, and additional organ support such as pressors or extracardiac membranous oxygenation (ECMO); and (8) death. Patients (0) to (3) were classified as mild cases, those with (4) to (5) as moderate cases, and those with (6) to (8) as severe cases.[4,16]

Statistical Analysis

Serum zinc concentration categories were defined according to the following criteria based on the treatment guideline for zinc deficiency published by The Japanese Society of Clinical Nutrition: deficiency (< 60 μg/dL), marginal deficiency (≥ 60 to < 80 μg/dL), and normal (≥ 80 μg/dL).[17]

Results are presented as means ± standard deviation (SD) for continuous variables or prevalence (%) for categorical variables. For comparisons between two groups (mild/moderate vs severe), Student's *t*-test was used for continuous variables, and the chi-squared test was used for categorical variables.

Serum zinc concentrations were compared between mild and other severity with Dunnett's method. P-values for trend were estimated using the Jonckheere-Terpstra test.

Serum zinc concentration levels were divided into two groups [marginal deficiency (≥ 60 to < 80 μg/dL)/normal (≥ 80 μg/dL), and deficiency (< 60 μg/dL)]. The association between severity (severe) and serum zinc level (deficiency) was identified using odds ratios (ORs) and 95% confidence intervals (CIs), with univariate logistic regression analysis and two multivariate models providing adjusted odds ratios (AORs) and 95% CIs. Model 1 was adjusted for age (years) and sex. Model 2 was adjusted for age (years), sex (male), BMI (kg/m^2), alcohol consumption (usual), smoking behavior (current), diabetic medication (yes), dyslipidemia medication (yes), and hypertension (yes), which were known as risks of aggravation of COVID-19 by Japanese Guidelines of COVDI-19.

$P < 0.05$ was considered significant. All statistical analyses were performed using the Statistical Package for Social Sciences, version 22 (SPSS Inc., Chicago, IL, USA).

Ethical Considerations

The Ethics Committee of Juntendo University approved using retrospective data for research related to with COVID-19 (No H20-0036). In addition, the Ethics Committee of Juntendo University reviewed and approved the research protocol of the study using retrospective data (No E21-0039). Informed consent was obtained in the form of opt-out on the website according to guidelines of the Ethics Committee of Juntendo University.

This survey was conducted in compliance with the Ethical Guidelines for Epidemiological Studies established by the Japanese Government[18] and in accordance with the Declaration of Helsinki of 1975 (revised in 2000).[19]

Results

Mean ages (SD) of the severe cases (n = 40) and mild/moderate cases (n = 427) were 68.1 (13.0) and 58.8 (18.3) years, respectively (Table 1). Severe cases had significantly higher mean heart rate, casual blood glucose concentration, LDH, BUN, CRP, and WBC relative to the mild/moderate cases. The proportions of those taking antihypertensive, antidiabetic, and antidyslipidemic medications and with CKD were significantly higher in the severe cases than in the mild/moderate cases. On the other hand, the serum zinc concentration level was significantly lower in severe cases than in mild/moderate cases [51.9 (13.9) vs 63.2 (12.3) μg/dL].

The proportions of subjects with serum zinc deficiency (< 60 μg/dL) and marginal zinc deficiency (≥ 60 to < 80 μg/dL) were 39.5% and 54.3% in women, and 36.4% and 57.0% in men, respectively (Figure 1).

In Model 1, serum zinc deficiency (< 60 μg/dL) was significantly associated with severe cases compared to marginal deficiency and normal (≥ 60 μg/dL) (AOR = 2.97, 95% CI = 1.45–6.06, P < 0.01). Those variables other than zinc such as BMI, smoking status and alcohol consumptions which were defined as risks of aggravation by Japanese Guidelines of

Table 1 Participants' Characteristics (N=467)

	Mean (SD) or N (%) Severity		P
	Mild and Moderate (n = 427)	Severe (n = 40)	
Age (y)	58.8 (18.3)	68.1 (13.0)	<0.01
Sex (male)	276 (64.6)	29 (72.5)	0.32
Anthropometric measurements			
Body mass index (kg/m^2)	24.6 (4.7)	25.5 (4.3)	0.30
Vital signs			
Blood pressure			
Systolic blood pressure (mmHg)	129.6 (19.7)	134.3 (18.7)	0.70
Diastolic blood pressure (mmHg)	82.3 (13.6)	81.4 (12.0)	0.15
Heart rate (per min)	87.0 (17.9)	91.3 (18.4)	0.15
Respiratory rate (per min)	18.4 (4.9)	23.4 (8.4)	<0.01
Temperature (°C)	37.0 (0.8)	37.3 (1.1)	0.13
Habits			
Alcohol consumption (usual)	207 (48.8)	16 (40.0)	0.29
Smoking behavior (Current)	74 (17.3)	5 (12.5)	0.44
Hypertensive medication (yes)	155 (36.3)	26 (65.0)	<0.01
Diabetic medication (yes)	85 (19.9)	16 (40.0)	<0.01
Casual blood glucose (mg/dL)	118.3 (44.9)	150.9 (67.2)	<0.01
Hemoglobin A1c (%)	6.1 (1.1)	6.4 (1.3)	0.09
Dyslipidemia medication (yes)	119 (27.9)	20 (50.0)	<0.01
Total cholesterol (mg/dL)	171.3 (37.8)	161.3 (41.3)	0.13
High-density cholesterol (mg/dL)	46.0 (13.8)	41.8 (14.4)	0.09
Low-density cholesterol (mg/dL)	97.7 (30.5)	90.6 (37.0)	0.20
Triglycerides (mg/dL)	125.6 (95.6)	124.4 (66.2)	0.94
Biochemical test			
Total protein (g/dL)	6.9 (0.6)	6.3 (0.6)	<0.01
Albumin (g/dL)	3.8 (0.5)	3.3 (0.5)	<0.01
Uric acid (mg/dL)	4.7 (1.7)	4.8 (2.1)	0.98
Lactate dehydrogenase (U/L)	221.4 (64.3)	355.8 (127.7)	<0.01
Blood urea nitrogen (mg/dL)	16.2 (12.2)	21.5 (14.8)	0.01
Creatinine (mg/dL)	1.1 (1.6)	1.6 (2.8)	0.05
eGFR (mL/min/1.73 m^2)	77.2 (26.6)	69.6 (34.5)	0.10
C-reactive protein (mg/dL)	3.3 (4.1)	8.3 (6.5)	<0.01
Ferritin (ng/mL)	579.3 (600.4)	973.3 (1019.2)	0.03
Zinc (μg/dl)	63.2 (12.3)	51.9 (13.9)	<0.01
Complete blood cell count			
White blood cell count	5.1 (1.9)	6.7 (3.5)	<0.01
Hemoglobin (g/dL)	14.2 (1.8)	13.4 (2.3)	0.01
Platelets	196.9 (70.0)	173.7 (73.1)	0.06
D-Dimer (μg/mL)	2.5 (5.3)	3.5 (3.5)	0.27
Organ damage/cardiovascular disease			
Heart	18 (4.2)	3 (7.5)	0.41
Brain	13 (4.2)	3 (7.5)	041
Chronic kidney disease	40 (9.4)	13 (32.5)	<0.01
Cancer	54 (12.7)	7 (17.5)	0.39
Chronic Obstructive Pulmonary Disease	44 (10.3)	7 (17.5)	0.18

Abbreviations: N, number; SD, standard deviation; eGFR, estimated glomerular filtration rate.

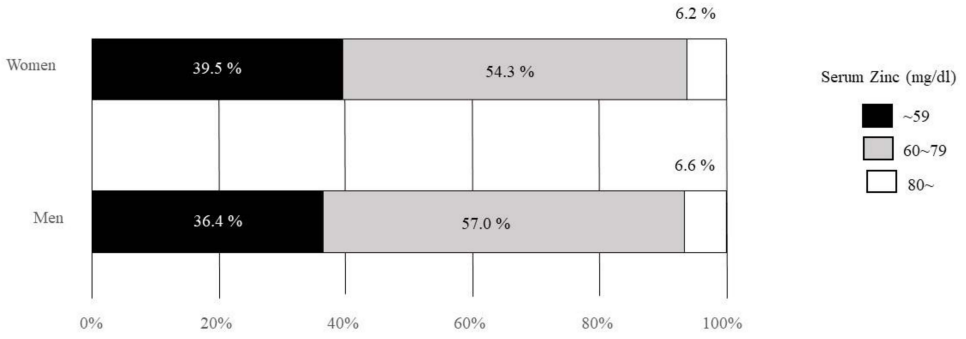

Figure 1 Proportion of zinc concentration levels.

COVDI-19 were not significantly associated. In Model 2, serum zinc deficiency was also significantly associated with severe cases compared to marginal deficiency and normal (AOR = 3.60, 95% CI = 1.60–8.13, P <0.01) (Table 2).

Figure 2 shows the relationships between severity of COVID-19 and serum zinc concentrations. An increase in severity of COVID-19 was inversely related to increases in serum zinc concentrations (P < 0.01 for trend). Each serum zinc concentration of moderate and severe cases was also significantly lower compared with mild cases (P < 0.01).

Discussion

The present cross-sectional study showed a relatively high proportion of serum zinc deficiency in COVID-19 cases. The serum zinc deficiency (<60/μL) was significantly associated with severe cases compared to marginal deficiency and normal levels (≧60μ). In addition, the severity of COVID-19 was significantly related to serum zinc concentration levels. Mean heart rate, casual blood glucose concentration, LDH, BUN, CRP, WBC, the proportions of those taking antihypertensive, antidiabetic, and antidyslipidemic medications and with CKD were significantly higher in severe cases.

Table 2 Factors Associated with Severe COVID-19 (Logistic Regression Analysis)

	Mean (SD[a]) or N[b] (%)	Univariate			Multivariate					
		OR[c]	95% CI[d]	P	Model 1[f]			Model 2[g]		
					AOR[e]	95% CI[d]	P	AOR[e]	95% CI[d]	P
Serum zinc concentration (μg/dL)										
Marginal deficiency and normal (≥ 60 μg/dL)	292 (625)	Reference			Reference			Reference		
Deficiency (< 60 μg/dL)	175 (37.5)	3.92	1.96–7.81	<0.01	2.97	1.45–6.06	<0.01	3.60	1.60–8.13	<0.01
Age (y)	57.6 (18.2)	—	—		1.04	1.01–1.06	<0.01	1.03	1.00–1.06	0.04
Sex (male)	305 (65.3)	—	—		1.74	0.82–3.68	0.15	1.49	0.62–3.54	0.37
Body mass index (kg/m^2)	24.7 (4.7)	—	—		—	—		1.05	0.96–1.14	0.26
Alcohol consumption (Usual)	223 (48.1)	—	—		—	—		0.71	0.31–1.59	0.40
Smoking behavior (Current)	79 (16.9)	—	—		—	—		0.92	0.31–2.68	0.87
Diabetic medication (yes)	101 (21.6)	—	—		—	—		2.08	0.92–4.72	0.08
Dyslipidemia medication (yes)	139 (29.8)	—	—		—	—		1.39	0.57–3.37	0.47
Hypertensive medication (yes)	181 (38.8)	—	—		—	—		1.30	0.51–3.30	0.59

Notes: a: standard deviation, b: number, c: odds ratio, d: 95% confidence interval, e: adjusted odds ratio, f: Model 1 was adjusted for age (years) and sex, g: Model 2 was adjusted for age (years), sex, body mass index (kg/m^2), alcohol consumption (usual), smoking behavior (current), diabetes medication (yes), dyslipidemia medication (yes), and hypertensive medication (yes).

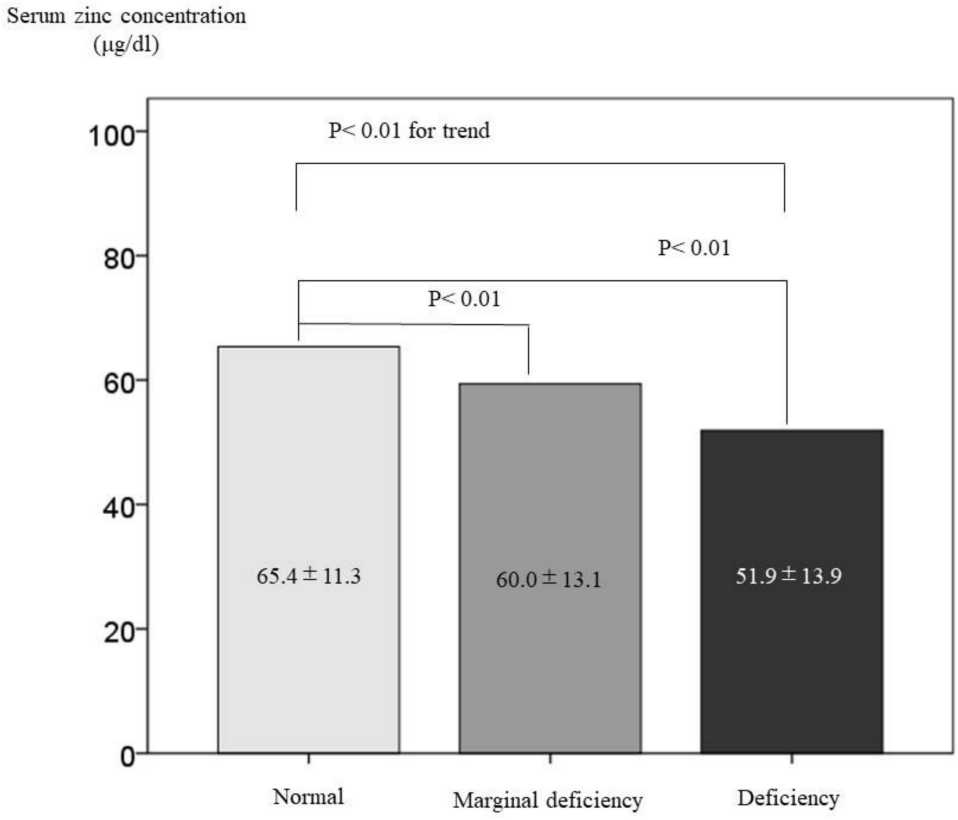

Figure 2 Relationships between severity of COVID-19 and serum zinc concentrations. Serum zinc concentrations were compared between mild and other severity with Dunnett's method. P-values for trend were estimated using the Jonckheere-Terpstra test.

Those variables such as BMI, smoking status and alcohol consumption which were defined as risks of aggravation of COVID-19 by Japanese Guidelines of COVDI-19, were not significantly associated in the multivariate regression model. To the best of our knowledge, only a few studies have investigated serum zinc levels and examined the association between serum zinc levels and severity in Japanese COVID-19 cases. In addition, the present study was conducted in a single facility which admitted patients of each degree of severity that reflected the real-world data of the center of a metropolitan city. Thus, the present study offers a novel insight on this matter.

The present results showed a relatively high proportion of serum zinc deficiency in COVID-19 cases. Our previous report examined serum zinc concentrations and characteristics of zinc deficiency/marginal deficiency in 2056 Japanese subjects who underwent voluntary health checkups; the proportions of subjects with serum zinc deficiency (< 60 μg/dL) and marginal zinc deficiency (≥ 60 to < 80 μg/dL) were 0.4% and 46.0% in men and 0.6% and 38.4% in women, respectively.[20] Thus, the proportion of serum zinc deficiency in COVID-19 cases seems to be relatively high compared to our previous study participants without COVID-19. Regarding the association between low serum zinc concentration and COVID-19, several clinical epidemiological studies have been reported.[21,22] A prospective study that examined COVID-19-infected patients in India at the time of hospitalization reported that COVID-19 patients (n = 47) showed significantly lower serum zinc levels than healthy controls (n = 45): median 74.5 (interquartile range 53.4–94.6) μg/dL vs 105.8 (interquartile range 95.65–120.90) μg/dL (P < 0.001), and that 57.4% of COVID-19 patients were serum zinc deficient (< 80 μg/dL).[21] A Brazilian observational study reported median serum zinc levels of 59.8 (49.7–67.7) μg/dL in 269 COVID-19-infected patients, and the prevalence of low zinc levels (< 70 μg/dL) was 79.6%.[22] These reports seem similar to the present results, and it is possible that these results suggest the necessity of considering serum zinc concentrations in the assessment of patients with COVID-19.

Related to the above discussion, the present data also show a significant relationship between severity of COVID-19 and serum zinc concentration levels. An epidemiological evaluation that included 275 French patients with COVID-19

showed that the median blood zinc level was significantly lower in patients with a poor clinical outcome (death or transfer to ICU or hospitalization for 10 days; N = 75) compared to patients with a good clinical outcome (other than the above; N = 200) (840 μg/L versus 970 μg/L; P < 0.0001).[23] A prospective study also reported that COVID-19 patients with zinc deficiency were found to have higher rates of complications (P = 0.009), acute respiratory distress syndrome (18.5% vs 0%, P = 0.06), corticosteroid therapy (P = 0.02), prolonged hospital stay (P = 0.05), and increased mortality (18.5% vs 0%, P = 0.06). The odds ratio (OR) of developing complications was 5.54 for zinc-deficient COVID-19 patients.[21] It has been reported that Zn deficiency disrupts endothelial barrier cell function in vitro and that status was corrected with Zn supplementation so that those results might explain one of the mechanisms of ARDS (Acute Respiratory Distress Syndromes) since 1995.[24] In fact, several previous reports have indicated the possibility of high-dose zinc supplementation having an effect as COVID-19 treatment. A meta-analysis that included five studies with 1506 participants in case and control groups reported that zinc supplementation in cases led to a significantly lower risk of mortality compared with the control group; the pooled OR (95% CI) was 0.57 [0.43, 0.77] (P < 0.001).[25] Therefore, it is possible that these results suggest an association between the serum zinc concentration and severity of COVID-19.

There are several other possible mechanisms to explain the association between severity of COVID-19 and serum zinc concentration levels. First is the immune system disturbance due to serum zinc deficiency. The role of zinc in immune system functions has been recently explored, and it is widely known that zinc is one of the main micronutrients in human health and nutrition.[26] Zinc regulates basic cellular functions such as DNA replication, RNA transcription, cell division, and cell activation.[27] Therefore, the macrophage, which is an essential cell in many immunologic functions, is adversely affected by zinc deficiency, and it can deregulate intracellular killing, cytokine production, and phagocytosis.[27,28] In addition, the generation of proinflammatory cytokines including IL-1β, IL-6, and TNFα is increased in zinc deficiency, and zinc deficiency leads to T cell lymphopenia, thymic atrophy, decreased numbers of premature and immature B cells, and decreased antibody generation.[28,29] In fact, a previous report examined the correlations between the serum zinc level at admission, the IL-6 level at admission, the highest value of IL-6 during the episode, and C-reactive protein, and found robust negative correlations between the zinc level and the levels of these inflammatory markers.[22] As zinc has one of the essential roles in oxidative burst and self protection,[30] zinc deficiency may occur proceeded to the acceleration of zinc consume after intense cytokine storm caused by COVID-19 tissue disorder.

Second is malnutrition due to COVID-19. Several clinical epidemiological studies reported a high proportion of malnutrition in patients with COVID-19. A single-center, retrospective study examined 116 French patients and reported that malnutrition, which was diagnosed by low body mass index (BMI) and weight loss ≥ 5% in the previous month and/or ≥ 10% in the previous six months, was found in 42 (38.9%) patients, with moderate or severe nutritional risk in 83 (84.7%) patients.[31] An observational, longitudinal study that included 114 French adult patients with COVID-19 showed that the overall prevalence of malnutrition defined by Global Leadership Initiative on Malnutrition (GLIM) criteria was 42.1% (moderate: 23.7%, severe: 18.4%).[32] Related to the above discussion, it is possible that malnutrition may be associated with zinc deficiency. The Tromsø Study, which was a cross-sectional, population-based survey that examined 1521 community-living elderly persons, reported that zinc deficiency was positively associated with the risk of malnutrition after adjusting with confounders (OR = 2.2; 95% CI 1.3, 3.6).[33] Although nutritional status could not be examined in detail in the present study, the data showed that serum TP and Alb concentrations were significantly lower in the severe group than in the mild and moderate group. Thus, it is possible that serum zinc deficiency due to malnutrition may be related to the severity of COVID-19. Nutritional screening and assessment including serum zinc levels may be necessary for patients with COVID-19 to plan the treatment strategy.

The present study has several limitations worth noting. First, it was subject to selection bias. This was a single-center study with a limited number of patients requiring hospitalization for COVID-19. Further analyses involving more diverse cohorts are necessary. Second, some key data were not collected, such as detailed information on the inflammatory and immune systems including cytokines, and assessment of the actual inflammatory and immune system status was limited. Further analyses collecting the details of key data are necessary. Third, some lifestyle-related criteria were vague because this information was collected from existing questionnaires. In addition, the information was collected using a self-administered questionnaire. Further comprehensive studies to collect the details of lifestyle characteristics are needed. Fourth, this study had a cross-sectional design, and thus causal relationships between serum zinc level and COVID-19 severity could not be evaluated; this is a critical limitation of the present study. Further analyses of follow-up survey data will be needed to address this issue.

Conclusion

The results of the present study showed that serum zinc deficiency was significantly associated with severe cases of COVID-19 compared to marginal deficiency and normal levels. In addition, the severity of COVID-19 was significantly related to the serum zinc concentration. These results suggest the importance of considering the serum zinc concentration in the treatment of patients with COVID-19.

Data Sharing Statement

Data will be available on request to the corresponding author.

Ethics Approval and Informed Consent

The Ethics Committee of Juntendo University approved using retrospective data for research related with COVID-19 (No H20-0036). In addition, the Ethics Committee of Juntendo University reviewed and approved the research protocol of the study using retrospective data (No E21-0039).

Informed consent was obtained in the form of opt-out on the website according to guidelines of the Ethics Committee of Juntendo University.

This survey was conducted in compliance with the Ethical Guidelines for Epidemiological Studies established by the Japanese Government and in accordance with the Declaration of Helsinki of 1975 (revised in 2000).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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